

### Olanzapine-induced mania in bipolar disorders

A study published in the *Archives of General Psychiatry* in September 2000<sup>1</sup> and a subsequent review<sup>2</sup> reported that olanzapine was more effective than placebo in the treatment of acute bipolar mania.<sup>1,2</sup> In spite of this documented antimanic efficacy, olanzapine might also result in a paradoxical effect: the induction of a manic episode. We describe here a patient with bipolar disorder who experienced a manic episode that was apparently induced by olanzapine. This case raises questions concerning the way in which this drug should be used in patients with this condition.

A 57-year-old man with type 1 bipolar disorder and a strong history of manic episodes had been well maintained on a regimen of amisulpride (200 mg/d) and lithium sufficient to maintain a lithium plasma level of 0.8 mmol/L. However, the neuroleptic had to be discontinued because of sexual side effects. The amisulpride was replaced with olanzapine (5 mg/d). At that time, the patient was euthymic. Within 1 week, acute mania had developed and the patient was experiencing irritability, psychomotor agitation, delusions of grandeur and insomnia. This state necessitated admission to hospital, where the olanzapine was stopped and the previous medication regimen reinstated. The manic episode resolved over the next 4 weeks.

We have observed similar cases of apparent risperidone-induced mania in euthymic bipolar pa-

tients, to whom this drug was given as a substitute for low doses of classical neuroleptics.

Aubry et al<sup>3</sup> recently reviewed cases of risperidone- and olanzapine-induced hypomania and mania identified by a MEDLINE search of the literature up to 1999. None of the olanzapine-induced episodes occurred in patients with bipolar disorder.

The main pharmacological characteristic of these atypical antipsychotic drugs is their higher potency as 5-HT<sub>2A</sub> serotonin receptor antagonists than as D<sub>2</sub> dopamine receptor antagonists. Lane et al<sup>4</sup> have suggested that risperidone-induced mania is related to dose. Low doses may result in blockade of 5-HT<sub>2A</sub> but not D<sub>2</sub> receptors. The antagonism of the 5-HT<sub>2A</sub> receptors would then lead to disinhibition of frontal dopamine release, which might account for the induction of manic episodes. It would be interesting to determine whether a similar mechanism is responsible for the effects of olanzapine. Although the hypothesis of Lane et al<sup>4</sup> about the occupancy ratio of 5-HT<sub>2A</sub> and D<sub>2</sub> receptors is attractive, it only partly fits the data from published case reports, in that most of the patients were receiving high doses of risperidone.<sup>3</sup>

Another mechanism has recently been proposed to account for frontal dopamine release induced by atypical antipsychotics:<sup>5</sup> combined blockade of both 5-HT<sub>2A</sub> and D<sub>2</sub> receptors promotes the ability of 5-HT<sub>1A</sub> receptor stimulation to increase frontal dopamine release. Therefore, the functional status of the serotonergic system is critical

for the effects of these drugs on frontal dopamine release. Our case report suggests that olanzapine may have differential effects in patients with bipolar disorder, depending on the state of endogenous neurotransmitter release. In some circumstances, changes in endogenous transmitter release may account for changes in drug effects; for instance, a partial agonist may act as an agonist when endogenous transmitter release is low and as an antagonist when endogenous transmitter release is elevated.<sup>6</sup> On the other hand, the balance between the activities of the dopaminergic and serotonergic systems might be impaired during manic episodes, which would result in an altered occupancy profile of the 5-HT<sub>2A</sub> and D<sub>2</sub> receptors, and therefore in differences in the psychopharmacological effects of these mixed drugs, according to the hypothesis of Lane et al.<sup>4</sup> Moreover, patients with bipolar disorder exhibit constitutive alterations in serotonergic tone and function,<sup>7</sup> even when they are euthymic. These alterations may account for the differential efficacies of atypical antipsychotics on serotonin signalling in patients with and without bipolar disorder and therefore on frontal dopamine release, according to the hypothesis of Ichikawa et al.<sup>5</sup>

From a practical point of view, this case provides some indications about appropriate management of changes in atypical antipsychotics in patients with bipolar disorder. Amisulpride was stopped on the same day that olanzapine was introduced. How-

ever, this seemed a reasonable approach, as the patient had been receiving a very low dose of amisulpride (6 times lower than that allowed during manic episodes or in schizophrenic patients), and the withdrawal of antipsychotics is usually not associated with the occurrence of manic episodes.<sup>3</sup> Moreover, the replacement of one classical antipsychotic with another does not typically trigger this kind of side effect. Thus, it seems important to point out this particularity to determine how best to use novel antipsychotics in bipolar disorder. Additional investigation will be needed to understand the mechanisms underlying their paradoxical effects.

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